REMARKS

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 16-8, 22-26, 30-34 and 36, the only claims pending and currently under examination in this application following entry of the above requested amendments.

Solely in order to expedite allowance of the present application, Claims 16 and 30 have been amended to limit the target of the drug moiety to a protein target, support for this amendment being found in now canceled Claim 21. In addition, the wording of several of the claims has been amended for clarification purposes. No new matter has been introduced to the application by the above amendments. As such, the Examiner is respectfully requested to enter the above amendments.

As indicated above, the above amendments have been made solely in order to expedite allowance of the present application. The above amendments should not in any way be construed as an agreement by the Applicants with the Examiner's position, and the Applicants expressly reserve the right to pursue claims of the original scope in one or more continuation applications.

The objection to Claim 31 has been addressed by the above amendment.

Claim 21 was rejected under 35 U.S.C. § 112, 2nd ¶. In view of the cancellation of this claim, this rejection may be withdrawn.

Claims 16-17, 21-22, 23, 24-25, 30-21 (?), 30-33 , 34 and 36 were first rejected under 35 U.S.C. §102 (b) over Pinchon, for assertedly being anticipated by Pinchon's disclosure of ODN-p-KDEL molecules and uses thereof.

As amended, the drug moiety of the claimed bifunctional molecules is one that binds to a protein target. Pinchon's molecules have a drug moiety, i.e., the ODN, that binds to a nucleic acid target.

As such, Pinchon does not anticipate the claims because Pinchon does not disclose a bifunctional molecule having a drug moiety that binds to a protein target.

Accordingly, Claims 16-17, 21-22, 23, 24-25, 30-21 (?), 30-33 , 34 and 36 are not anticipated under 35 U.S.C. §102 (b) by Pinchon and this rejection may be withdrawn.

Next, Claims 16-18, 21-26, 30-34 and 36 continue to be rejected under 35 U.S.C. §102 (b) as being anticipated by the WO 95/10302 published application.

For purposes of review, the claims are limited to methods of directing a drug to an intracellular space or site. The goal of the claimed methods is accomplished by limiting the bifunctional molecule to one in which the drug is conjugated to a targeting moiety that binds to intracellular protein. As such, excluded from the claims are methods of directing a drug to an extracellular site, where the bifunctional molecule includes a targeting moiety that binds to an extracellular protein.

As explained in the Applicants' previous response, the conjugates disclosed by the WO 95/10302 published application are conjugates of a first binding member and a second binding member, where the second binding member binds **to a long-lived blood component**, i.e., to an **extracellular protein** that is present in blood, e.g., albumin. Furthermore, the WO 95/10302 published application is explicitly directed only to methods of maintaining a drug in an extracellular space. In other words, the WO 95/10302 application is exclusively directed to methods of directing a bifunctional molecule to an extracellular space, and not to an intracellular space. Throughout the disclosure of the WO 95/10302 application, the target binding member is a member that binds to a long-lived blood component. As such, the WO 95/10302 published application

does not teach or even suggest a method of directing a molecule to an intracellular space, much less by using a bifunctional molecule in which the ligand component of the molecule binds to an intracellular protein.

In attempting the rebut the Applicants' position, the Examiner states:

"...The WO 95/10302 publication teaches other binding (targeting) entity such as steroid Estrogen (See page 10, lines 35-36, in particular), TSH, LH, FSH or their agonist (See page 25, lines 17-19, in particular) wherein the targeting moiety 'will be selected to bind to its complementary binding member,' for example, the steroid will bind to the respective steroid receptor which is an intracellular protein (See page 10, lines 35-36, in particular). As such, the reference steroid receptors are specific biodistribution modulating protein that locates in the intracellular space such as the cytoplasm."

From the above passage, the Examiner appears to misread the WO 95/10302 reference as disclosing bifunctional molecules where estrogen, TSH, LH or FSH are the targeting moiety for the molecule. However, upon careful review of this reference, this reference does not teach such molecules.

First, page 10, lines 35 to 36 of the reference states:

"...the conjugate will be selected to bind to its complementary binding member, as compared to the number other molecules which may be....

Nowhere is the word estrogen found in this passage. In fact, the text of the corresponding 440 patent has been searched for the word estrogen, and the word estrogen appears nowhere in the text. As such, it is unclear how this passage supports the Examiner's interpretation.

Furthermore, while page 25, lines 17-19 does disclose TSH, LH and FSH, this disclosure is limited to two component embodiment of the disclosed approach for

attaching a target to a long lived blood component which is the subject of the cited reference. Specifically, one embodiment of the invention of the cited reference is to have two compounds administered to a host, where the first compounds includes a moiety that binds to the target agent and the second compound includes a moiety that binds to the long lived blood component, specifically to an extracellular moiety of the long lived blood component.

The passage cited by the Examiner on page 25 is merely referring to mechanisms for joining the first and second compounds in a stable fashion in an extracellular space. For example, the cited passage first discloses avidin/biotin as a potential way to join the two compounds extracellularly. The passage then goes on to state that alternatives to avidin/biotin including TSH, LH, FSH and their receptors. As such, these moieties are merely taught as members of a specific binding pair in a two compound system which is still used to bind a target agent to an extracellular protein present on a long lived blood component.

As such, contrary to the Examiner's reading, WO 95/10302 does not disclose a bifunctional molecule in which a drug moiety is conjugated to an intracellular protein binding moiety. Where bifunctional molecules that include the TSH, LH and FSH moieties are described, they are not bifunctional molecules that also include a drug moiety for a protein target, but are bifunctional molecules that include moiety for an extracellular long lived blood component target. As such, these moieties do not teach the claimed bifunctional molecules. Similarly, in those bifunctional molecules that include a receptor for the numerous agents listed on page 5, lines 5 ff, the molecules fail to include both a drug moiety and a moiety for binding to an intracellular protein, as required in the pending claims.

Because the WO 95/10302 published application fails to teach or even suggest a method of directing any molecule to an intracellular space, much less by administering the bifunctional molecule as one that includes a ligand component that binds to an intracellular protein, it clearly does not anticipate Claims 16-8, 21-26, 30-34 and 36,

which claims include the limitation that the methods are for directing a drug to an intracellular site and that the ligand bind to an intracellular protein.

As such, WO 95/10302 fails to anticipate Claims 16-8, 21-26, 30-34 and 36 under 35 U.S.C. §102 (b) and this rejection may be withdrawn.

Claims 16-18, 21-26, 30-34 and 36 were also rejected under 35 U.S.C. §102 (e) as being anticipated by U.S. Patent No. 5,843,440. This patent contains the same disclosure as the above discussed WO 95/10302 application. As such, for the reasons provided above, the 440 patent also fails to anticipate the claims. Accordingly, Claims 16-8, 21-26, 30-34 and 36 are not anticipated under 35 U.S.C. §102 (e) by U.S. Patent No. 5,843,440 and this rejection may be withdrawn.

Finally, the Examiner has maintained the rejection of 16-8, 21-26, 30-34 and 36 under 35 U.S.C. § 103(a) as being obvious over either WO 95/10302 or U.S. Patent No. 5,843,440 in view of U.S. Patent No. 5,830,462, asserting that the only difference between the claimed methods and the primary references is the size of the bifunctional molecules, which element is made up by the `462 patent.

However, as pointed out above, the primary references are fundamentally deficient in that **they do not teach or suggest methods of directing a drug to an intracellular space by administering the drug as a bifunctional molecule that includes a ligand for an intracellular protein, and the combination of these references with the 462 teaching of size does not teach such a bifunctional molecule.**

In the Examiner's reiterated summary of what the `462 patent teaches, the Examiner makes a number of statements that indicate that the Examiner may have misunderstood the teaching of this reference. For example, the Examiner indicates at the bottom of page 5 of the office action that bifunctional molecules of less than 5 kd are taught in the `462 patent because this patent teaches chimeric fusion proteins of

FkBP12 and a tryosine kinase, FK506 fused to a DNA binding domain. However, these are fusion proteins and, as such, have a molecular weight far in excess of 5 kD. The Examiner also finds a disclosure of targeting to specific locations by pointing to the teaching of targeting the chimeric proteins to particular locations. However, this is targeting of chimeric fusion proteins already present in the host, not of a drug moiety administered to the host. There is no teaching in the patent of targeting the bifunctional inducers of dimerization to any particular location. Furthermore, the Examiner makes the statement that the `462 disclosure is directed to methods of modulating biodistribution of a drug. However, nowhere in the patent is the term "biodistribution" or an analogous word provided, because the patent is not directed to methods of modulating biodistribution, but to a much more complicated system of effecting a biological response.

Specifically, the cited supplemental 5,830,462 patent is directed to a system in which engineered chimeric fusion proteins present in a subject are brought together by an administered bifunctional chemical inducer of dimerization to cause a desired effect that only occurs when the two chimeric proteins are brought together. In the system disclosed in the `462 patent, the subject must be genetically engineered to include the chimeric fusion proteins that respond to the later administered bifunctional molecule inducers of dimerization.

As such, the purpose of the system of the `462 patent is completely different from the purpose of the primary references. While the primary references are directed to methods of anchoring a third molecule to a long-lived blood product by using a bifunctional molecule that includes a ligand for the long lived blood product and a ligand for the third molecule, the `462 patent is directed to methods of inducing dimerization of two chimeric proteins that are inside of a cell. As such, the two disclosures are directed to entirely different areas of a host, the first being directed to extracellular locations and the second being directed to intracellular locations.

Contrary to the Examiner's reading there is no motivation among the references for one to modify the primary references to target to an intracellular protein, because no utility do so is provided. It would defeat the purpose of the primary references to swap out the long lived blood component ligand and it would not accomplish the purpose of the secondary reference because such a substitution would not result in the desired dimerization of the chimeric proteins.

Accordingly, contrary to the Examiner's reading, one would not be motivated by the combined teaching of the references to produce bifunctional molecules as employed in the presently claimed methods, much less to practice the claimed methods.

Because the `462 patent fails to teach directing a drug to any location, much less an intracellular location, by administering it as a bifunctional molecule and the Examiner has only cited this patent for its teaching of small sized bifunctional molecules, this reference fails to make up the fundamental deficiencies in the primary references as discussed above. Accordingly, the combined teachings of the WO 95/10302 or 5,843,440 references in view of the 5,830,462 reference fails to teach or suggest the claimed methods.

Because the combined teachings of the WO 95/10302 or 5,843,440 references in view of the 5,830,462 reference fails to teach or suggest the claimed methods, Claims 16-18, 21-26, 30-34 and 36 are not obvious under 35 U.S.C. § 103 over these references and this rejection may be withdrawn.

CONCLUSION

In view of the above remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance. The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815.

Respectfully submitted,

Date: March 18, 2003

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